Policy Perspectives from Members of the Bioethics Community
Pilar Ossorio, Ph.D., J.D.

DR. WILLARD: Our next speaker is Dr. Pilar Ossorio. She's an assistant professor of law and medical ethics at the University of Wisconsin Law School and is also an associate director in the Center for the Study of Race and Ethnicity in Medicine at the University of Wisconsin Law School.

Thank you very much for being with us.

DR. OSSORIO: Thank you, and I do have some slides, so it's okay, I'll just say next slide, and we can go to the next two. There we go.

I'm going to talk about reporting results back to participants, and I should say that Professor Greely and I are both involved in a project at Stanford University in their Center for Excellence in Ethics, where we have a working group that has been discussing this particular set of issues very intensively. We will be coming out with a white paper soon, and I suspect that you will all eventually get that white paper. Some of the things I'm going to say today I will actually highlight as the results of those discussions and where we've come seemingly to a consensus, and others are my personal analysis and I'll try to highlight that.

So I wanted to start just by highlighting some sort of background conditions and assumptions, things that I understand about the proposed project here, importantly that it's going to measure a lot of environmental exposures. It's not just going to be about gene sequencing but it's going to measure environmental exposures. Probably ultimately some people will have a lot of gene expression work, proteomics, epigenetics done, so there will be, at least for some participants at some point, almost something like total cellular characterization that will be associated with lots and lots of not just medical data but other data. So you will have people who have biological material in a repository along with more data than most people would ever have in their medical record.

This means that inevitably you will find out medically, clinically important things about people as you go through this project.

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I also want to think about this, somewhat separating the issues in terms of building the resource, that is collecting specimens and data initially, and then follow-on studies. That would be studies done by people who are using the resource. The reason to do that is because I think there might be, in general, some differences in those two categories, differences that are ethically important and that have a pragmatic sort of impact on what you might do. Those differences involve the proximity of researchers to participants both in space and time. So people doing follow-on studies, people might develop clinically relevant information, but they might be crunching data five years after the data and material were collected.

The fact that it's five years later that you found something clinically relevant and that you may not have any interpersonal relationship, the follow-on researcher may never have met any of these participants, was not the person who collected biological specimens from any of them, that may influence the ethical obligations or the permissibility even of reporting back any of this information.

Follow-on studies may be more likely to generate information that's not yet validated, and they may also be subject to the regulatory regimes in slightly different ways, which would affect how difficult it is to go back and report information. So I think we need to realize that there's a lot of complexity here, because there's a whole set of issues around reporting back information when you're first building the resource, and there's a somewhat separate set of issues about reporting back information from people who are doing follow-on studies.

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So the first thing I want to say is Francis mentioned earlier this morning that there are lots of people who have thought about this issue, there are lots of papers, a number of different policy reports, including one that the Secretary's Advisory Committee on Genetic Testing, I think, put out, a number of policy committees that have studied this and made recommendations. There's not much consensus, actually, and I think that some of the issues that this proposed project raises are issues that really haven't been addressed fully, or not addressed at all by the proposals that are out there.

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So there's the obvious spectrum of practices and proposals. At one end of that spectrum is not returning any individualized results, and I should say that right now I'm very much focusing on the return of individualized results to individual participants, as opposed to aggregate results to a community of people, or even aggregate results returned to participants individually. I'm assuming that there will be some felt obligation to return, to make publicly known and available the aggregate results of research done with such a project. So that's one of my background assumptions.

So we're really talking about individual results, and in fact the practice of most genetic studies up until now has been not to return individual results, and that's partially because a lot of these studies we weren't yet collecting any information that had been validated that was viewed as clinically useful, and the practice of not returning results was initiated in that context. But now things have changed, and so people's views about the permissibility of not returning individual results I think is beginning to change, and in this project, as I mentioned before, you aren't just going to have genetic information. You may have lots of other clinically relevant information where the clinical utility of it might be very well known.

But at that end of the spectrum, don't return results, that's where most genetic studies have been. That's where a lot of IRBs have been. So a lot of IRBs are very reluctant to approve protocols where individual genetic results are going to be returned.

Of course, beyond that end of the spectrum you have everything from sort of a very limited set of clinically relevant results might be returned to almost any clinically relevant information. One big battle that we're having in the working group is where does reproductive information fit in, or with respect to genetics where does carrier information fit in. It may be very important to people. In their lives, their reproductive choices may be as important as their personal life or death medical decisions, but a lot of the ethics guidelines that are out there, to the extent that they discuss returning results, either don't treat reproductive information as the kind of results that are very important or that must be returned, or they just don't talk about them separately at all.

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So I thought I would just take one moment to say that there are good reasons not to return individual results. First of all, I think if there's any unanimity with respect to genetics, in particular it's that you ought not to be returning results unless they're clinically validated; that is, unless, first of all, they have been analytically validated, but also that we know something about the relationship of having a particular allele to a particular medical outcome.

There's good reason. The balance of harm and benefit is likely to tilt towards not returning results when you don't really know the meaning of those results. The costs of sharing results when they're ambiguous, when you don't know their implications, are going to be higher. A lot more education will have to go into that, a lot more difficulty in interpreting the results, and so forth. So I think there are good reasons for not returning clinically validated results.

Also by not returning results you're increasing opportunities to maintain confidentiality and privacy protections. To the extent that you return results, you have to have linking information back to individuals, and you have potentially a number of people getting in contact with them from research projects.

Again, this issue of sort of the relationship between the researcher and the participant. In cases where there's no direct personal contact of any sort, the value of reciprocity, of some kind of mutual obligation, mutual sharing, tends not to be weighed as strongly certainly by researchers, but I would suspect by participants as well. Secondly, the information may be already outdated in some way. The person may have already discovered it. If you don't find it out until five years after they gave material and information, they may already have found this out, for instance. So some people would say that if it's distant in time and space, that there is less of an incentive ethically or otherwise to provide the information.

I think the final thing, and this is important, is that not returning back results helps to maintain the kind of cognitive and legal distinction between research and the provision of medical care. What we've been talking about this morning I think in some ways, for some of the researchers, is going to very much blur that line between the provision of clinical care and the doing of research, and sometimes it creates conflicting obligations that are very, very hard to reconcile for the researcher him or herself, and a lot of confusion for the participant about what it is that they are going to get out of this project.

I think there are lots of ethically permissible possibilities in there, but we need to get really clear, you need to get really clear, about where you see the lines drawn in terms of what the project would provide to people and what it wouldn't, and then be able to very clearly communicate those boundaries, because we already know that participants in research have a lot of confusion about the distinction between research and medicine.

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So going on to say that it's pretty clear that a project of this sort will almost certainly have to return at least some results. Then you get into the really interesting questions, which are which results, to whom, how, what is the process of returning them, and when would you do it?

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I would reiterate that there's a pretty wide agreement among researchers, among ethicists, among all the policy recommendations, that results shouldn't be returned unless there is some analytic and clinical validity. For sure, analytic validity. I think legally there would have to be -- at some

point in returning results it has to go through a CLIA-approved lab, although I am very aware that many researchers believe that their lab does a much better job than the CLIA-approved lab to which they sometimes send their specimens. But nonetheless, legally that would have to come in there somewhere.

But clinical validity as well. Again, I would say there's fairly broad agreement that we don't return results when we don't really know what they mean.

There are lots of reasons in favor, and I tend to think about this set of issues as there's going to be a very, very small domain of research results, if any domain of research results, where it is obligatory to return those results. There will be a much wider domain where it will be permissible to return those results. We have reasons in favor, perhaps reasons against, both ethical and pragmatic. So it's going to be a weighing and balancing. But if you look at all the recommendations and the kinds of things we were coming to agreement on in this working group at Stanford, it would be when the results have very serious medical implications for the participant directly, when there's an urgency about knowing these results, when the results would change the medical management in some way. So there is a certain debate. What if you find something very serious but there is nothing that can be done about it? Are those the kinds of results that ought to be reported back?

I think there are reasons in favor, but there are more reasons in favor of reporting back results where it's both serious and you could do something about it. Where there's a more robust relationship, like a face to face relationship between the participant and the researcher, and the value of reciprocity is greater, their expectations of what you will do on their behalf is greater, and it won't come as a surprise if some complete stranger drops in on them and says, oh, by the way, I found this out about you and it's really important for your medical care; and then as a matter of respect for participants. I put that in because there's not a lot of research on what participants want in terms of getting results back, but there are some surveys and a few interviews, and mostly they show that participants have a fairly high degree of interest in getting results back, and also in the few instances where at least genetic results are being given back, mostly we haven't seen real harms coming from that, although anecdotally there are certainly anecdotes and individual instances, not so much from genetics but from other areas of medicine and other areas of clinical research, where people have gotten back clinically relevant results and found it to be very burdensome and maybe something that they wished they hadn't learned.

So participants are going to have a range of views about what results they might want back and a range of experiences if they do get results back, and there's not a lot of data out there on this right now. But I do think that the data we have suggests that many participants would like at least some results back.

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So going on, which results would we give back? There are a number of interesting questions that are raised. One of them is whether the nature of the research gives ethical or other kinds of reasons for returning back results. For instance, does it matter whether you're doing a study to look for a particular gene/environment interaction, like you're doing a study looking at prostate cancer, and you find something clinically relevant about prostate cancer that a person probably doesn't know? Or what if you're doing a study about prostate cancer and you find genetic information suggesting that the person is likely to have long QT syndrome or has an oncogenic BRCA1 mutation?

When you're doing these big studies, there will be people who have a significant portion of their genome sequenced, and you will find something in their genome that is clinically relevant, and it may not be anything that was the particular subject of the study initially. So if you're going to report back results, does it matter whether it was an incidental finding in the context of these very, very large studies? What does incidental even mean if you're doing non-hypothesis-driven research?

In the working group, my belief is based on recent phone calls that we've had that there is at least a category of research for which it wouldn't matter, or a category of results that are seemingly so important for a person clinically that it wouldn't matter whether they were incidental findings or findings that were sort of as the direct focus of your research that they might need to be reported back. Does it matter that in these very large studies it's foreseeable that you will find something, or if this is something that nobody ever foresaw? Those might be different categories to which you would attach different degrees of permissibility or obligation to report.

Also, another question that, at least in our working group, we debated a lot is do researchers ever have a duty to look around for clinically relevant information? So if we've got sequenced data that was just churned out by a machine, does somebody have an obligation to go look and see what your BRCA1 allele or other clinically relevant alleles, what you have? There wasn't agreement about that. The way we currently do research, it wouldn't be hard to put a query into the computer to look for all of these things, but different individuals you're going to find different clinically relevant things, and we couldn't come to agreement about whether or not there was a duty to actually go searching for clinically relevant information.

My own personal feeling about this is that there's not and we ought not to set that on researchers.

Also, is there a right not to know? Almost all of the ethics guidelines would say that there is a right not to know, but interestingly, many clinical researchers say no, and I can tell you that in front of our IRB we get people who say I would not have someone in my study if they said don't give me back clinically relevant information. I think the dividing line here is really people who are clinicians and who, in the course of their research, have contact with participants or are doing a clinical exam. Their feeling is if I find something incidental or something I was looking for that's clinically relevant, it's my obligation to tell this person, and partly that's because they're in a context where their duties as a physician and their duties as a researcher are both coming to the fore, whereas many of the people who are doing sequencing or other kinds of cellular analyses are not physicians, they're not having direct personal contact, and they're feeling that I see something in these data but I don't really relate them to a person, I don't have any connection to that person, diminishes their belief that they ought to report back clinically relevant results no matter what.

Whether that relationship should make this much of a difference is a matter of debate. Some people think it should not. I think as a practical matter, it does.

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So our working group is going to end up proposing three categories of results that would have different degrees of obligation or permissibility with respect to reporting back, and that's not so different from a couple of previously published papers. Other groups have come up with some similar kinds of recommendations.

So category 1 would be results, whether they're genetic or other kinds of results, that you would be obliged to report back. It wouldn't matter what the focus of the research was, and it wouldn't matter who was doing the research, whether they were doing follow-on research or what, that these results would be perceived as so important that you would report them back. There was really, as I said, no agreement on whether there's an obligation to actually go searching for that kind of information, but I think many people felt there was not.

Category 2, which would be a very broad category, would be things that it might be permissible to report back, but it's discretionary. One thing about this category is that to the extent that you're going to do it, we felt and many other groups have felt that you have to plan for it up front, have it in the protocol, have the IRB see it, have it in the consent form, again to delineate very clearly what they might get back, what kinds of future contacts they might have from researchers if they choose to participate, and so forth.

There is a category 3, which would be information that is not permissible to report back.

Category 1 might only include really very, very few things.

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So we had the three categories, and that addresses the question of what kind of information should you report back, and in category 1 are things that are so important to someone's health and their health care decision making now that you would report them back. Everything else is either discretionary or impermissible to report. Then the question is how, and the method would depend somewhat on the category. So we felt for all categories, if it's going to be reported back, it has to be approved by an IRB, included in consent, and it has to be reported back by a person with relevant expertise, and in a project like this that could be quite complicated because different people will have different alleles that might be medically relevant. It won't just be one person or two or three or four people who are associated with the project who would have that expertise, and that's just the genetics. What if you have some other finding?

Think about it. What if you find that some group of people is having a very toxic exposure to some chemical in their neighborhood or in their work environment? You might find that in such a project where you're collecting a lot of environmental information. How would you report that back, and to whom, and would it just be to the participants? There are going to be a lot of issues there, and you need people with relevant expertise to do it, and figuring out who those people are when a lot of different kinds of expertise may be relevant is going to be difficult. We didn't go so far as to figure out the nitty-gritty details of this, but one of the things it suggests is that the more you want to report back, the more expensive it's going to be, the more personnel you would need dedicated to this process in some way or another, maybe not full time.

Of course, for genetics, it has to at some point be validated in a CLIA-approved lab. We didn't exactly agree on when and with what specimens. So we actually came to agreement that there are a range of possibilities of when in the process of reporting back it would go to a CLIA-approved lab.

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There's also the question of how. What kinds of contacts? We figured for category 1, the initial contact might be by phone or by letter. However it happened, it ought to invite people to contact you and have a discussion about a clinically relevant finding, and it ought to be formulated in

such a way that they knew that there was something serious, and that it had to be followed up. So if you make some initial contact and people don't call or write in or make any attempt to really follow up and find out about the clinically relevant information, that there is a fairly strong obligation on the researchers to follow up, try second contact, make sure they really got the letter or received the phone call, and it was a person and not just a phone machine.

Every effort must be made to have face to face delivery of information when the actual discussion of the clinically relevant information takes place, and there's no obligation to provide follow-up medical services, but at a minimum you should be able to provide referral information.

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DR. WILLARD: Will you, perhaps in the next few minutes, wrap up please?

DR. OSSORIO: Sure.

I guess I would go just on category 2, we thought that there might be the need for something like a DSMB or a similar kind of committee to help researchers decide, in that permissible category, when at least some results were actually at the level of significance that they ought to be reported back.

DR. LEONARD: What is a DSMB?

DR. OSSORIO: A data safety monitoring board.

DR. LEONARD: Thank you.

DR. OSSORIO: Next slide, please.

There are also questions about when. Again, this comes back to what happens if you have data sitting around somewhere and then years later somebody finds out, oh, there's some real medical significance attached to a particular allele? Do you have to go back and continue to review the data that you have to see how new information affects the significance of the existing data? There are lots of questions about that that we didn't come to agreement on, but I'm just going to highlight them now to say they're actually important questions and you need to come to some agreement on them.

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I'm going to skip that one and go to the very last slide, I think. Actually, this is not the last slide. There was agreement that you ought to give participants options, and the options ought to include reporting back to the participant and/or reporting back to the doctor or primary care provider or somebody like that. They also ought to have the option of not getting information back. Although some clinicians didn't like that, at least our working group thought, and most ethicists believe, that there is something like a right not to know.

With respect to families, there was pretty strong agreement that there is no obligation to give this information to families, but that it ought to be spelled out for participants that this information is important to their family members, and that ought to be part of the discussion and the follow-up.

Next slide, please, which I believe now is the last. Yes. So I just wanted to sum up, then, in my last slide that a lot of this is about what will be permissible rather than what will be obligatory. So you're going to have tradeoffs, because reporting back is going to add a lot of cost. The more you report back, the more cost it's going to add. So there are tradeoffs between your desire to report back and to create benefit for people by doing that, and the amount of data you can collect, the number of participants you can have in a study, et cetera.

Also, the issues of reporting back intersect with the issues about who you include. So on the one hand if you include people who are not insured or have very little access to medical care, does it ever provide a benefit? There's debate about that. For instance, you might end up creating more constituencies who are pushing for more things to be covered by Medicaid or Medicare, for instance. On the other hand you might report back something of real clinical relevance to somebody when they couldn't do anything about it, and they would view that as much more of a harm than a benefit.

Finally, I would say also this is where your consultations and interactions with communities, your community engagements, could help formulate the project with respect to within those bounds of permissible reporting back, what kind of information might people most want, and under what conditions and things like that. It actually gives a lot of opportunity for ethics experimentation, as well as scientific experimentation.

And I will stop.

DR. WILLARD: Thank you, Dr. Ossorio.